

REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

Claims 21 and 28 have been amended. Claims 21-26, 28-29 and 52-57 are in the case and are before the Examiner.

A. The Amendments

Claim 21 was amended to more clearly recite the claimed invention. Claim 28 has been amended to depend from claim 53, rather than claim 27 that had been cancelled previously.

It is thus seen that no new matter has been added.

B. Rejections Under 35 USC §103(a)

1. Bergh et al In View of Schachter et al.

Claims 21-23, 25, 52, 54 and 56 have been rejected under Section 103(a) as allegedly obvious from the combined teachings of Bergh et al. US Patent No. 4,925,796 (hereinafter Bergh) in view of Schachter et al. *Methods in Enzymology* (hereinafter Schachter). The Action asserts that Bergh discloses the use of a fucosyltransferase along with GDP-fucose for the fucosylation of oligosaccharides of glycoproteins. Bergh does not, however, include the claimed GDP-fucose forming enzymes, as is noted in the Action. The Schachter teaching is used to provide the nucleoside-diphospho fucose forming enzyme (fucose pyrophosphorylase), although it actually teaches use of a unseparated mixture of that enzyme and a fucose kinase for forming fucose 1-phosphate.

Thus, the only pertinent disclosures of Bergh are to the single transferase enzyme, GPT-fucose and a fucosyl acceptor. Schachter provides disclosure of formation of fucose 1-phosphate using an impure nucleoside-diphospho fucose-forming enzyme and a fucose kinase. Based on those two disclosures, the present claims are said to be obvious. This basis for rejection cannot be agreed with and is respectfully traversed.

Schachter teaches the preparation of GDP-fucose using separated reaction mixtures and isolations with no suggestion to use a single vessel. As noted before, the Schachter paper teaches that the two enzymes there present (kinase and nucleoside-diphospho fucose forming enzyme) are utilized separately in that fucose kinase is precipitated and separated from the remainder of the preparation **prior** to the preparation of GDP-fucose using the prepared fucose 1-phosphate, GTP and the GDP-fucose forming enzyme. (See, paragraph bridging pages 286-287, first sentence.)

It is reiterated that Schachter separated the kinase enzyme and its reaction from the nucleoside-diphospho fucose forming enzyme and its reaction. Schachter used two different reactions and vessels. It is submitted that that separation taught by Schachter teaches away from the subject matter of claims 23-25 that are rejected here over a combination of disclosures that included Schachter without reservation. Thus, on this basis alone, this rejection as to claims 23-25 should be withdrawn, as should the broader rejection recited above.

Additionally, there is neither teaching nor suggestion that the two enzymes recited in claim 21 would be compatible. Indeed, in native form, the fucosyltransferase is membrane-bound (page 18, first sentence), and therefore may interact with the

Serial No. 09/992,680

GDP-fucose forming enzyme. That point is underscored in Dr. Paulson's accompanying Declaration.

As will be seen, Dr. Paulson points out that the enzymes involved in the claims do not naturally occur together in the same compartment in eukaryotic cells. Instead, the fucosyltransferase is inside the Golgi apparatus, the GDP-fucose and GDP-mannose forming enzymes are in the cytoplasm so that the enzymes are separated by a membrane. The finished GDP-fucose is transported into the Golgi apparatus, and the GDP product is exported back into the cytoplasm. Dr. Paulson also notes that the two cellular two compartments are documented to be quite different from each other in pH, reducing environment, and the like. Those facts led Dr. Paulson, a worker of more than ordinary skill in this art, to conclude that there was no way for a worker of ordinary skill in this art at the time this invention was made to know if the enzymes and their respective substrates were compatible with each other in an *in vitro* environment until tried. In a more colloquial view, if "Mother Nature" separated the enzymes, reactants and products, there must have been a reason.

In view of the Action's having provided no teaching or suggestion in the relied-on art that the two recited enzymes would be compatible together, and Dr. Paulson's expert conclusion that a worker of ordinary skill at the time this invention was made could not predict that the two recited enzymes would be compatible and that the skilled worker would be more apt to believe that those enzymes, their substrates and products to not be compatible, there was not the reasonable expectation of success required by *In re Vaeck* 947 F.2d 488, 493; 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). This rejection should again therefore be withdrawn.

Still further, Claim 21 recites that the nucleoside-diphospho fucose-forming enzyme is present in a catalytic amount. There is again neither teaching nor suggestion that such an amount be present. Indeed, Schachter that is relied-on for teaching the use of that enzyme utilizes a reaction mixture containing 27 micromoles of substrate β -L-[¹⁴C]fucose 1-phosphate in 300 ml of buffer to which 150 ml of the enzyme preparation are admixed to achieve an average of a 60% yield over two hours of reaction. It hardly seems that that amount contains a catalytic amount of enzyme, as compared to more of a stoichiometric amount.

The much larger amount of nucleoside-diphospho fucose-forming enzyme present in the Schachter disclosure that catalyzed that reaction is not relevant to a claim that recites a "catalytic amount" of the enzyme. It is submitted that there is a vast difference to a skilled worker between a stoichiometric amount of enzyme that catalyzes a given reaction and a catalytic amount of that enzyme. There is also a lack of teaching or motivation to shift from the higher to the catalytic amount. It is submitted that the absence of this recited limitation or its suggestion cannot be glossed over as has been done in the Action. Again, therefore, this rejection should be withdrawn.

2. Bergh In View of Schachter, and

Further in View of Demain et al.

Claims 21-25, 52, 54, 55 and 57 were also rejected as allegedly obvious over the above-discussed teachings of Bergh and Schachter further in view of Demain et al. US Patent No. 4,178,210 (hereinafter Demain). The Bergh and Schachter teachings were taken as described before and the Demain teaching

Serial No. 09/992,680

was said to disclose the use of ATP in the regeneration of pyruvate kinase, which was said to have pertinence here because "Schachter's process requires ATP... ." It was thus asserted that

"the artisan of ordinary skill would have considered the use of the well-known PEP/pyruvate kinase ATP regeneration system an obvious method of regenerating the ATP required for the ultimate synthesis of the GDP-fucose required in Bergh's fucosylation process."

This basis for rejection again cannot be agreed with and is therefore, respectfully traversed.

The deficiencies of the combination of the disclosures of Bergh and Schachter in regard to independent claim 21 have already been discussed and are again repeated here by reference. As such, and inasmuch as independent claim 21 is seen to be patentable over the combined teachings of those disclosures, the Demain teaching adds nothing as to claim 21 and cannot make any of the dependent claims obvious. Thus, this rejection should be withdrawn.

Additionally, the rejected independent claim does not require an "ATP regeneration system", nor is such a system recited. Furthermore, ATP is not used in a GDP regenerating system disclosed herein, and is not seen "to be required for the ultimate synthesis of the GDP-fucose required in Bergh's fucosylation process." Further, although the pyruvate kinase system is known to "require" ATP, ATP is not claimed, nor is it required as is asserted in the Action. Thus, the Demain teachings are not seen to have any

Serial No. 09/992,680

relevance here and Demain should be withdrawn as a reference against the claims along with this rejection.

3. Bergh In View of Schachter and Demain, and
Further in View of Yamamoto et al.

Claims 21-26, 28, 29 and 52-57 were rejected as allegedly obvious over the combined teachings of Bergh, Schachter and Demain as already discussed and further in view of the teachings of Yamamoto et al. (hereinafter Yamamoto). Yamamoto is cited for its disclosure of a NADH/NADPH regenerating system and the preparation of GDP-fucose from GDP-mannose that is recited in dependent claim 26 and the conversion of GDP-mannose to GDP-fucose that are recited in claims 28 and 29.

The Action has once again mixed the page numbers of the Schachter and Yamamoto disclosures. The Action also misquoted from the relied-on art. It is therefore difficult to determine exactly the basis for the rejection.

For example, it is said that Yamamoto discloses "compositions comprising the claimed ingredients, including NADPH regenerating system (right column, page 283, lines 18-21),... ". As noted in the last Reply, Yamamoto begins on page 823, and Schachter begins on page 285.

The inadvertent errors of the Action notwithstanding, the Action asserts that having all of the enzymatic tools available, the worker of ordinary skill would have recognized solely from the recited art that those enzymes could be put together to provide a single composition. This basis for rejection cannot be agreed with and is respectfully traversed.

The deficiencies of the combination of the disclosures of Bergh and Schachter in regard to independent claim 21 have been discussed twice above and are repeated here by reference. The Demain teaching was shown to be irrelevant to the claimed subject matter. Independent claim 21 is patentable over those combined teachings, and the Yamamoto teaching adds nothing as to claim 21 and cannot make any of the dependent claims obvious. Thus, this rejection should be withdrawn.

4. General Argument

The Action agrees that neither Yamamoto nor Bergh, both of whom had the teachings of Schachter and Demain available to them as did Dr. Wong, put together the present invention. Taking all of the teachings together, they recite the enzymes and other constituents of the claims. If the claims were as obvious as asserted in the Action, Yamamoto had all of the elements and should have put it all together in 1984, or Bergh should have done it two years later in 1986, its filing date.

Neither group did so.

It took another five or seven years for the proper person, Dr. Wong, to put the pieces together. He got the motivation from somewhere and figured out that the enzymes could be compatible and all be present together with their substrates and other ingredients. Dr. Paulson's enclosed Declaration points out that a worker of ordinary skill would not have thought the various constituents to be compatible at the time Dr. Wong's parental application was filed in 1991. Dr. Paulson's Declaration also points to the lack of intuitive motivation prior to Dr. Wong's work here.

It is submitted that most things look obvious in hindsight. A hindsight reconstruction is just what is present

Serial No. 09/992,680

in this Action and these several bases for rejection. The various pieces have been found in scattered disclosures and put together in view of the application's own disclosures to make the invention appear to be obvious. It is submitted that the artisan of ordinary skill would recognize nothing in regard to these claims from the relied-on prior art and that only looking back with the present disclosure as a guide could one come to the present invention. This rejection should be withdrawn.

It is further submitted that even if were proper to take the necessary elements from the relied-on teachings and put them together, the result would not define the invention. There is no teaching in the relied-on art to use a catalytic amount of a nucleoside-diphospho fucose-forming enzyme. As such, the rejection must again fail for lack of establishing a *prime facie* case, and should be withdrawn.

C. Summary

Claims 21 and 28 have been amended. Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

A Notice of Appeal and its required fee are enclosed to permit the Examiner sufficient time to deal with this paper. No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

Serial No. 09/992,680

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By 

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Enclosures

Notice of Appeal and fee
Paulson Declaration and CV

CERTIFICATE OF MAILING

I hereby certify that this Amendment and Reply and its stated enclosures are being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on November 9, 2004.

By 
Edward P. Gamson



RESPONSE UNDER 37 C.F.R. §1.116
EXPEDITED PROCEDURE

EXAMINING

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Chi-Huey Wong et al.)
Serial No.: 09/992,680) PATENT
Filed: November 19, 2001) Attorney Docket
) SCRF-267.3 DI
) (3195/84503)
For: Production Of Fucosylated)
Carbohydrates By Enzymatic)
Fucosylation Synthesis Of) Group Art
Sugar Nucleotides; And In Situ) No.1651
Regeneration Of GDP-Fucose)
Examiner: Francisco C. Prats)

DECLARATION OF DR. JAMES C. PAULSON

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DR. JAMES C. PAULSON DECLARES:

1) That he is employed by The Scripps Research
Institute, of La Jolla, California, the assignee of the
subject application;

2) That a true copy of his Curriculum Vitae is
attached to this Declaration;

3) That at the time this invention was made he was employed by Cytel, Corp. as its Vice President of Research;

4) That the Cytel Corp. was engaged in research and development of potential treatments that utilized carbohydrate molecules such as those synthesized by the reaction of the claims;

5) That as part of his duties at Cytel, he was in part responsible for licensing the technology of the subject application as well as other technology developed by Dr. Wong alone or Dr. Wong and his co-workers, as well as technology from other research groups;

6) That the subject application is now licensed by Neose, Corp.;

7) That he is an advisor to Neose, Corp;

8) That he has read and is familiar with the application, the Action, including Examiner's remarks, and the art that forms the bases for rejection;

9) That he is the Paulson of the "Paulson et al. *J. Biol. Chem.*," cited at column 14, lines 57-58 of the Bergh et al. patent whose disclosures are relied upon in the Action.

10) That it is his recollection of the events at the time this and other inventions of Dr. Wong were made, that each new 'nucleotide-sugar cycle' completed by Dr. Wong and

his group was greeted by scientific community of workers of ordinary skill as another example in a remarkable series of related but independent achievements;

11) That each of the relied-on disclosures identifies individual enzymes and how they can be used independently of each other to either synthesize GDP-fucose or to carry out fucosylation using GDP-fucose;

12) That the enzymes involved in the claims do not naturally occur together in the same compartment in eukaryotic cells, rather,

a) the fucosyltransferase is inside the Golgi apparatus, and the GDP-fucose and GDP-mannose forming enzymes are in the cytoplasm,

b) the enzymes are thus separated by a membrane; and

c) the finished GDP-fucose is transported into the Golgi apparatus, and the GDP product is exported back into the cytoplasm.

13) That the two cellular two compartments are documented to be quite different from each other in pH, reducing environment, and the like;

14) That the Action's reliance at page 6 on the true statement that "GDP-fucose is continually synthesized by physiologically 'normal' cells containing numerous other enzymes, none of which interfere with each other to block

the synthesis" is misplaced because of the differences between cellular and *in vitro* manufacture of GDP-fucose and fucosylated products;

15) That because of the above-stated differences between cellular and *in vitro* manufacture of fucosylated products, the worker of ordinary skill at the time the claimed invention was made (using the first filing date of 1991 as that date for this paper) would have been more likely to expect interference between the enzymes, reactants and products than a lack of such interference and therefore would have required direct evidence of a lack of interference;

16) That there was no way for a worker of ordinary skill in this art to know if the enzymes and their respective substrates were compatible with each other in an *in vitro* environment until tried;

17) That in view of those differences, the motivation for putting the enzymes together is not intuitive and there was no motivation for a worker of ordinary skill at the time this invention was made to combine the relied-on teachings as has been done in the Action;

18) That it is his further view that the Action has made a hindsight reconstruction to match the teachings with the claimed invention;

19) That all statements made herein of his knowledge are true and all statements made on information and belief are believed to be true; and further, these statements were

made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.



James C. Paulson

11/08/04

Date

Enclosure: Curriculum Vitae

CERTIFICATE OF MAILING

I hereby certify that this Declaration and Curriculum Vitae, as well as the Amendment and Reply and its stated enclosures are being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Mail Stop AF Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on November 8, 2004.

By



Edward P. Gamson

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PROFESSIONAL POSITIONS:

1999-present Professor, Depts. Mol. Biol. & Mol. Exp. Med., The Scripps Research Institute, La Jolla, CA
1996-1999 Vice President, Chief Scientific Officer, General Manager Glytec Division, and Member Board of Directors, Cytel Corporation, San Diego, CA
1990-1996 Vice Pres. Res. And Dev. and Member of Board of Directors, Cytel Corp., San Diego, CA
1985-1990 Professor and Vice-Chair, Dept. of Biol.Chem., UCLA Sch. of Medicine, Los Angeles, CA
1981-1985 Associate Professor, Dept of Biol. Chem., UCLA School of Medicine, Los Angeles, CA
1978-1981 Assistant. Professor, Dept. of Biol. Chem., UCLA School of Medicine, Los Angeles, CA
1974-1978 Postdoctoral Fellow/Res. Assoc., Dept. of Biochem., Duke Univ. Med. Ctr, Durham, NC

EDUCATION:

University of Illinois at Champaign-Urbana
Ph.D. (Biochemistry)1974
M.S. (Biochemistry) 1971
MacMurray College, Jacksonville, Illinois
A.B.(Chemistry/Biology)1970

PROFESSIONAL ACTIVITIES:

2002-2003 President, The Society for Glycobiology
2001-present Principle Investigator, Consortium Functional Glycomics, <http://glycomics.scripps.edu/>
1999-present Scientific Advisory Board, Neose Technologies Inc
1996-present Honorary Member, American Society of Clinical Investigation
1990-present Editorial Board, Glycobiology
1990-present Member, American Chemical Society
1989-1999 Scientific Advisory Board, Complex Carbohydrate Resource Center, Univ. Georgia
1989-1991 NIH Study Section, Pathobiochemistry
1986-1988 Scientific Advisory Board, Nucleic Acid Research Institute
1985-1991 Editorial Board, Journal of Biological Chemistry
1980-present Member, American Society of Biological Chemists
1979-present Member, Society for Complex Carbohydrates

PATENTS AND PATENT APPLICATIONS:

Antigenic compositions and methods for using the same

Reiko F. Irie, Tadashi Tai, Donald L. Morton, Leslie D. Cahan, James C. Paulson

Patent issued December 10, 1985. #4,557,931

Method for producing secretable glycosyltransferases and other processing enzymes

James C. Paulson, Eryn Ujita-Lee, Beverly Adler, Jeffrey K. Browne, Jasminder Weinstein

Patents issued: #5,032,519, #5,541,083; #5,776,772

Process for controlling intracellular glycosylation of proteins.

James Paulson, Eryn Ujita-Lee, Jasminder Weinstein

Patent issued September 10, 1991 #5,047,335

Intercellular adhesion mediators

James Paulson, Mary Perez, Federico Gaeta, and Murray Ratcliffe

Patent issued May 19, 1998 #5,753,631

Compositions and methods for the identification and synthesis of sialyltransferases

James Paulson, Dawn Wen, Brian Livingston, Bill Gillespie, Sørge Kelm, Kati Medzerhadsky, Alan Burlingham

Patent issued January 12, 1999 #5,858,751; October 5, 1999 #5,962,294

Antibodies to P-selectin and their uses

Robert Chestnut, Margaret Polley and James Paulson

Patent issued September 1, 1998 #5,800,815

Use of trans-sialidase and sialyltransferase for synthesis of sialyl-2-3-betagalactosides

Yukishige Ito and James Paulson

Patent issued April 4, 1995, #5,409,817

Practical In vitro sialylation of recombinant glycoproteins

James C. Paulson, Eric Sjøberg and Bob Bayer

Patent issued June 4, 2002, #6,399,336

Control of Immune Responses by Modulating Sialyltransferases

Jamey Marth and James Paulson

Patent issued June 4, 2002, #6,376,475

Method for Detecting the Presence of P-Selectin

Robert Chestnut, Margaret Polley and James Paulson

Patent issued March 7, 2000, #6,033,667

Practical in vitro Sialylation of Recombinant Glycoproteins

James Paulson, Robert Bayer, and Eric Sjøberg

Patent issued June 4, 2002, #6,399,336B1

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24. Paulson, J. C. (1996). Leukocyte adhesion deficiency type II. In *Glycoproteins and Disease* (Montreuit, J., Vliengenthart, J. F. G. & Schachter, H., eds.), pp. 405-411. Elsevier Science B.V., Netherlands.
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